10/509078

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SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:           22 TO      418
PROJECTED ANSWERS:               0 TO        0

L2            0 SEA SSS SAM L1

=> s l1 sss full
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FULL SCREEN SEARCH COMPLETED -      163 TO ITERATE

100.0% PROCESSED      163 ITERATIONS                              19 ANSWERS
SEARCH TIME: 00.00.01

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L4           10 L3 AND NC>1

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FULL ESTIMATED COST                               180.20     180.41

FILE 'CAPLUS' ENTERED AT 19:54:20 ON 20 MAY 2007
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=> s l4
L5            7 L4

=> d l5 1-7 bib abs hitstr

L5   ANSWER 1 OF 7  CAPLUS  COPYRIGHT 2007 ACS on STN
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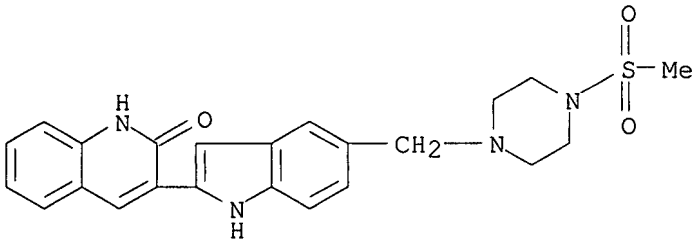
10/509078

AN 2007:82250 CAPLUS
DN 146:337707
TI Efficient Syntheses of KDR Kinase Inhibitors Using a Pd-Catalyzed Tandem C-N/Suzuki Coupling as the Key Step
AU Fang, Yuan-Qing; Karisch, Robert; Lautens, Mark
CS Davenport Chemistry Laboratories, Department of Chemistry, University of Toronto, Toronto, ON, M5S 3H6, Can.
SO Journal of Organic Chemistry (2007), 72(4), 1341-1346
CODEN: JOCEAH; ISSN: 0022-3263
PB American Chemical Society
DT Journal
LA English
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB A family of four potent KDR kinase inhibitors containing an indol-2-yl quinolin-2-one structure, e.g. I, utilized a Pd-catalyzed tandem C-N and C-C coupling sequence. The key step in preparation of I involved the Pd(OAc)2/(S)-Phos-catalyzed reaction of gem-dibromovinyl compound II with quinoline derivative III to give 86% indol-2-ylquinoline derivative IV.
IT 415684-58-1P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of KDR kinase inhibitors using a Pd-catalyzed tandem C-N/Suzuki coupling as the key step)
RN 415684-58-1 CAPLUS
CN 2(1H)-Quinolinone, 3-[5-[[4-(methylsulfonyl)-1-piperazinyl]methyl]-1H-indol-2-yl]-, hydrochloride (1:1) (CA INDEX NAME)



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RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:172057 CAPLUS
DN 142:411180
TI Synthesis of 5-Substituted-1H-indol-2-yl-1H-quinolin-2-ones: A Novel Class of KDR Kinase Inhibitors
AU Kuethe, Jeffrey T.; Wong, Audrey; Qu, Chuanxing; Smitrovich, Jacqueline; Davies, Ian W.; Hughes, David L.
CS Department of Process Research, Merck & Co., Inc., Rahway, NJ, 07065, USA
SO Journal of Organic Chemistry (2005), 70(7), 2555-2567
CODEN: JOCEAH; ISSN: 0022-3263
PB American Chemical Society

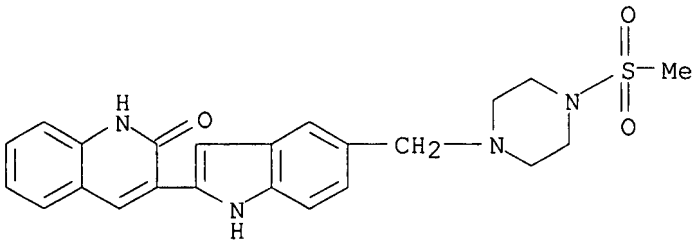
DT Journal
LA English
OS CASREACT 142:411180
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB A number of approaches for the synthesis of the 1H-indol-2-yl-1H-quinolin-2-one ring system found in the potent and selective KDR kinase inhibitor I are described. The preparation and reaction of trimethylsilylnitrobenzene II with 2-methoxy-3-quinolinecarboxaldehyde afforded alc. III, which was the key intermediate for the preparation of the target compds. Conversion of alc. III to either nitroketone IV or nitrostyrene V set the stage for reductive cyclization. The quinolin-2-one functionality was unmasked in the last step to provide compound I in 56-60% overall yield from readily available starting materials.

IT 415684-58-1P
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of 5-substituted 1H-indol-2-yl-1H-quinolin-2-ones via Fischer-indole cyclization, Pd-catalyzed annulation, and by reductive cyclization of nitro ketone or nitro styrene derivs.)

RN 415684-58-1 CAPLUS
CN 2(1H)-Quinolinone, 3-[5-[[4-(methylsulfonyl)-1-piperazinyl]methyl]-1H-indol-2-yl]-, hydrochloride (1:1) (CA INDEX NAME)



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RE.CNT 101 THERE ARE 101 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:857555 CAPLUS
DN 141:337784
TI Formulations for tyrosine kinase inhibitors
IN Karki, Shyam B.; Deshpande, Sameer R.; Thompson, Karen C.; Payne, Anne H.; Gandek, Thomas P.
PA Merck & Co. Inc., USA
SO PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004087651	A2	20041014	WO 2004-US8828	20040323
	WO 2004087651	A3	20041216		

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RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

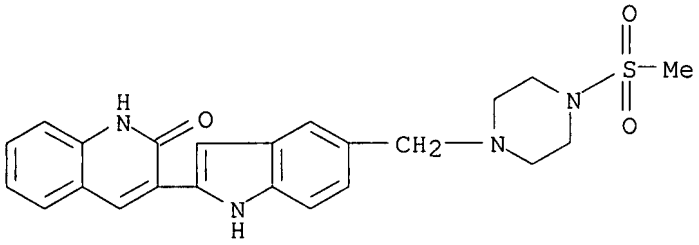
AU 2004225949	A1	20041014	AU 2004-225949	20040323
CA 2519106	A1	20041014	CA 2004-2519106	20040323
EP 1610614	A2	20060104	EP 2004-758216	20040323
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK				
CN 1764381	A	20060426	CN 2004-80007813	20040323
JP 2006521360	T	20060921	JP 2006-507476	20040323
US 2006093666	A1	20060504	US 2005-544213	20050802
PRAI US 2003-458094P	P	20030327		
WO 2004-US8828	A	20040323		

AB The present invention is related to a powder, powder blend or granulation formulation of 3-[5-(4-methanesulfonylpiperazin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one (I), a tyrosine kinase inhibitor, which is adapted for reconstitution with a diluent. This invention is also related to an aqueous suspension, or a dispersion, particularly to a stable oral pharmaceutical formulation, comprising granules of I mixed with a diluent. Thus, a formulation contained I 1080.0, Avicel PH101 800.0, lactose 1860.0, Klucel EXF 120.0, AcDiSol 120.0, and Mg stearate 20.0 mg/bottle.

IT 415684-58-1P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(formulations for tyrosine kinase inhibitors)

RN 415684-58-1 CAPLUS

CN 2(1H)-Quinolinone, 3-[5-[[4-(methylsulfonyl)-1-piperazinyl]methyl]-1H-indol-2-yl]-, hydrochloride (1:1) (CA INDEX NAME)



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L5 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2004:804130 CAPLUS

DN 141:424102

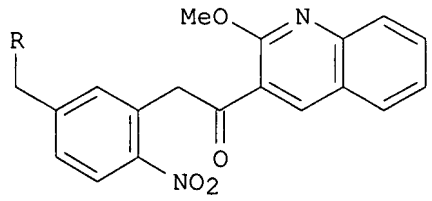
TI Synthesis of Novel KDR Kinase Inhibitors through Catalytic Reductive Cyclization of o-Nitrobenzylcarbonyl Compounds

AU Wong, Audrey; Kuethe, Jeffrey T.; Davies, Ian W.; Hughes, David L.

CS Department of Process Research, Merck & Co., Inc., Rahway, NJ, 07065, USA

SO Journal of Organic Chemistry (2004), 69(22), 7761-7764
CODEN: JOCEAH; ISSN: 0022-3263

PB American Chemical Society
DT Journal
LA English
OS CASREACT 141:424102
GI



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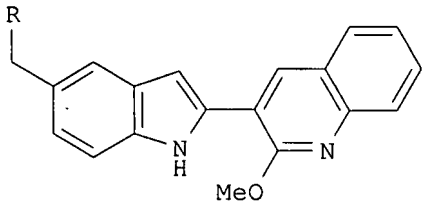

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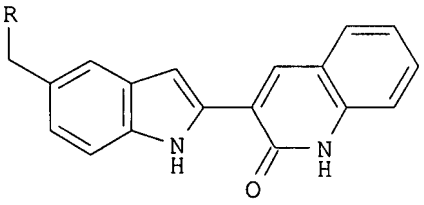


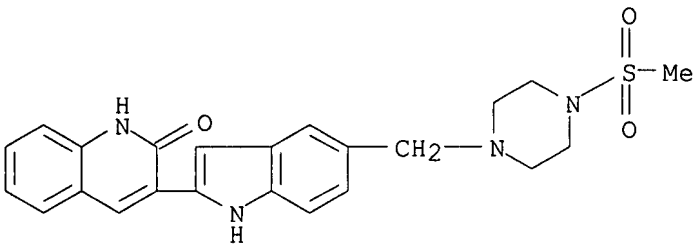
III

AB An efficient synthesis of o-nitrobenzylcarbonyl compds. by the Swern-type oxidation of readily accessible phenethanol analogs is reported. Reductive cyclization of o-nitrobenzylcarbonyl quinoline I [R = 4-(methylsulfonyl)piperazin-1-yl] using catalytic Raney nickel gives 1H-indol-2-yl-1H-quinoline II in 95% yield. Hydrolysis of II affords the KDR kinase inhibitor III in quant. yield. The analogous procedure was applied for the synthesis of indolyl quinolines II (R = H, MeCO2). The examination of the reductive cyclization reaction and optimization of conditions is described.

IT 415684-58-1P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of indolyl quinolines via catalytic reductive cyclization of nitrobenzylcarbonyl quinolines)

RN 415684-58-1 CAPLUS

CN 2(1H)-Quinolinone, 3-[5-[[4-(methylsulfonyl)-1-piperazinyl]methyl]-1H-indol-2-yl]-, hydrochloride (1:1) (CA INDEX NAME)



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RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2003:855752 CAPLUS
DN 139:354459
TI Solid forms of 3-[5-(4-methanesulfonyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one hydrochloride salt with tyrosine kinase activity
IN Karki, Shyam B.; Payack, Joseph; Treemaneekarn, Varaporn; Wang, Yaling; Sato, Yuichi
PA Merck & Co., Inc., USA; Banyu Pharmaceutical Co., Ltd.
SO PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003088900	A2	20031030	WO 2003-US11022	20030411
	WO 2003088900	A3	20040521		
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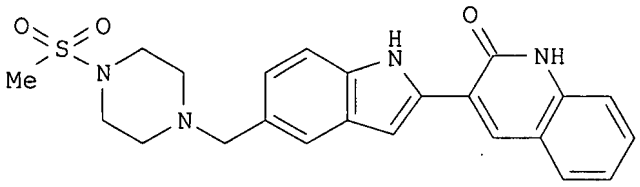
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2480325	A1	20031030	CA 2003-2480325	20030411
	AU 2003226051	A1	20031103	AU 2003-226051	20030411
	US 2005113577	A1	20050526	US 2003-506710	20030411
	JP 2005528400	T	20050922	JP 2003-585653	20030411
PRAI	US 2002-372782P	P	20020416		
	WO 2003-US11022	W	20030411		

GI

Apps



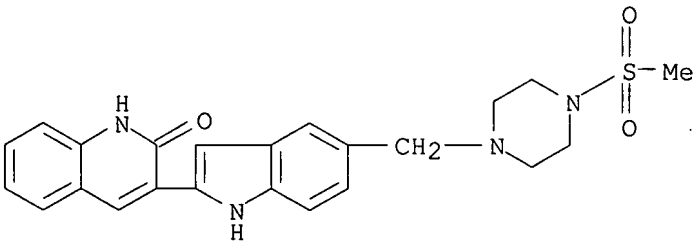
I

AB The present invention relates to solid forms of the I.HCl of which inhibit, regulate and/or modulate tyrosine kinase signal transduction, compns. which contain these compds., and methods of using them to treat tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals. I and its HCl salt were prepared and crystal forms were obtained and characterized.

IT 415684-58-1P
RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(solid forms of 3-[5-(4-methanesulfonyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one hydrochloride salt with tyrosine kinase activity)

RN 415684-58-1 CAPLUS

CN 2(1H)-Quinolinone, 3-[5-[[4-(methylsulfonyl)-1-piperazinyl]methyl]-1H-indol-2-yl]-, hydrochloride (1:1) (CA INDEX NAME)



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L5 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN

AN 2003:202621 CAPLUS

DN 138:238027

TI Preparation of 3-(2-indolyl)quinolin-2(1H)-ones as tyrosine kinase inhibitors

IN Peckham, Jennifer P.; Hoffman, William F.; Arrington, Kenneth L.; Fraley, Mark E.; Hartman, George D.; Kim, Yuntae; Hanney, Barbara; Spencer, Keith L.

PA Merck & Co., Inc., USA

SO PCT Int. Appl., 143 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI WO 2003020699 A2 20030313 WO 2002-US27114 20020826
WO 2003020699 A3 20030522
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
AU 2002323406 A1 20030318 AU 2002-323406 20020826
US 2004235826 A1 20041125 US 2004-487589 20040224
US 7186723 B2 20070306
PRAI US 2001-316123P P 20010830
WO 2002-US27114 W 20020826

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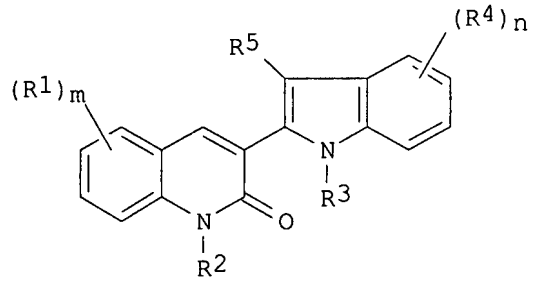

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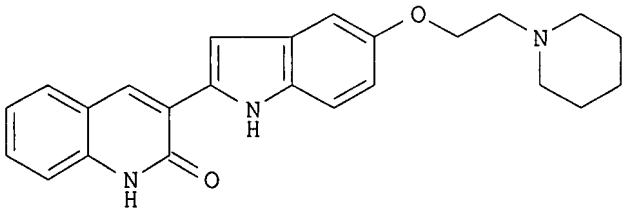


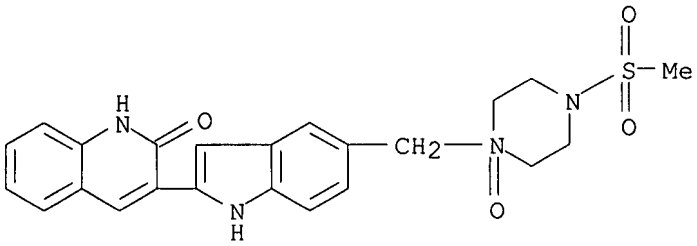
II

AB Title compds., including I (R groups undefined), were prepared and inhibitors, regulators, and/or modulators of tyrosine kinase signal transduction. For example, 1-(tert-butoxycarbonyl)-5-[(tert-butyldimethylsilyl)oxy]-1H-indol-2-ylboronic acid was coupled with 2-chloro-3-iodoquinoline (preparation of starting materials given) in the presence of Pd(PPh3)4 and K3PO4 in dioxane to give the protected 3-(2-indolyl)quinoline derivative Deprotection using triethylamine trihydrofluoride afforded the alc. Reaction with 1-(2-chloroethyl)piperidine•HCl and Cs2CO3 in DMF followed by reflux at 110° in AcOH and H2O for 12 h provided II. Compds. of the invention inhibited VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 values between 0.01 μM - 5.0 μM. Thus, I and compns. containing I are useful for the treatment of tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals (no data).

IT 501334-36-7P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(tyrosine kinase inhibitor; preparation of (indolyl)quinolinones for treatment of cancer, atherosclerosis, inflammatory diseases, and other tyrosine kinase-dependent conditions)
RN 501334-36-7 CAPLUS
CN Piperazine, 1-[[2-(1,2-dihydro-2-oxo-3-quinolinyl)-1H-indol-5-yl]methyl]-4-(methylsulfonyl)-, 1-oxide, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

CRN 335649-91-7
CMF C23 H24 N4 O4 S



CM 2

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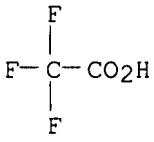

L5 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2002:314903 CAPLUS
DN 136:325437
TI Preparation of oxoquinolinylindole-5-methanamine salts as tyrosine kinase signal transduction modulators
IN Fraley, Mark E.; Karki, Shyam B.; Kim, Yuntae
PA Merck & Co., Inc., USA
SO PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002032861	A2	20020425	WO 2001-US32508	20011017
	WO 2002032861	A3	20020815		

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	AU 2002026877	A5	20020429	AU 2002-26877	20011017
	US 2002072526	A1	20020613	US 2001-981979	20011017
	US 6656942	B2	20031202		
	EP 1328519	A2	20030723	EP 2001-987742	20011017
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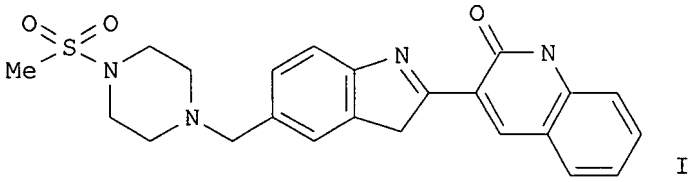
	ES 2247187	T3	20060301	ES 2001-1987742	20011017
	US 2004002501	A1	20040101	US 2003-398851	20030410
	US 6960590	B2	20051101		
PRAI	US 2000-241043P	P	20001017		
	WO 2001-US32508	W	20011017		

GI



I

AB Title compds. were prepared as tyrosine kinase signal transduction modulators (no data). Thus, di-protected 5-hydroxymethylindole-2-boronic acid was condensed with 3-iodo-2-quinolinone (preparation each given) and the O-deprotected product oxidized to the aldehyde which was reductively aminated by 1-methanesulfonylpiperazine to give, after deprotection and salt formation, title compound I.MeSO3H.

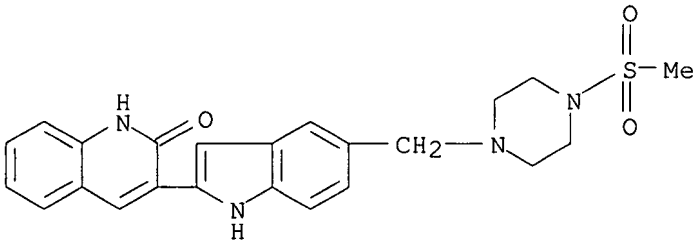
IT 415684-56-9P 415684-57-0P 415684-58-1P
415684-59-2P 415684-60-5P 415684-61-6P
415684-62-7P 415684-63-8P 415684-64-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of oxoquinolinylindole-5-methanamine salts as tyrosine kinase signal transduction modulators)

RN 415684-56-9 CAPLUS

CN Piperazine, 1-[[2-(1,2-dihydro-2-oxo-3-quinolinyl)-1H-indol-5-yl]methyl]-4-(methylsulfonyl)-, monomethanesulfonate (9CI) (CA INDEX NAME)

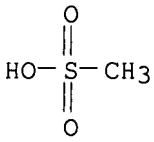
CM 1

CRN 335649-90-6
CMF C23 H24 N4 O3 S



CM 2

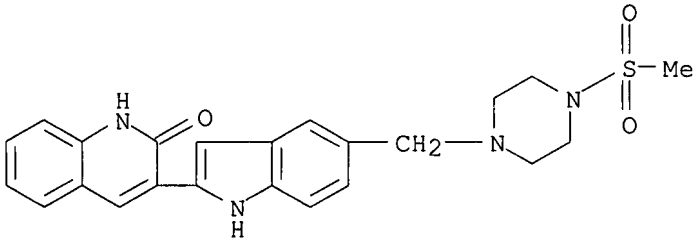
CRN 75-75-2
CMF C H4 O3 S



RN 415684-57-0 CAPLUS
CN Piperazine, 1-[[2-(1,2-dihydro-2-oxo-3-quinolinyl)-1H-indol-5-yl]methyl]-4-(methylsulfonyl)-, (2R,3R)-2,3-dihydroxybutanedioate (9CI) (CA INDEX NAME)

CM 1

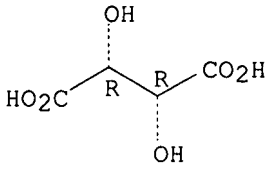
CRN 335649-90-6
CMF C23 H24 N4 O3 S



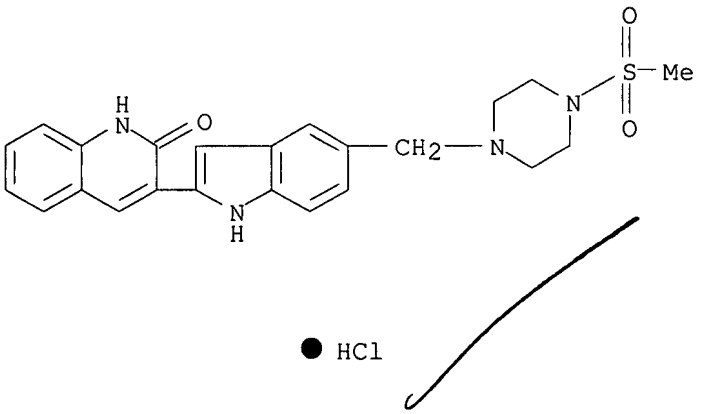
CM 2

CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.



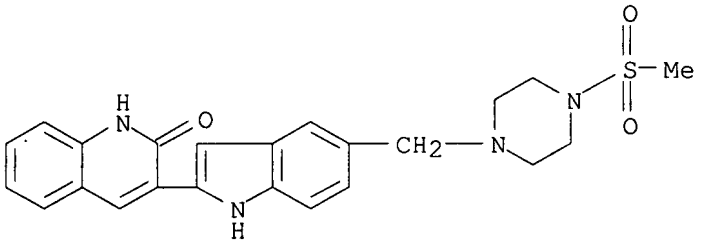
RN 415684-58-1 CAPLUS
CN 2(1H)-Quinolinone, 3-[5-[[4-(methylsulfonyl)-1-piperazinyl]methyl]-1H-indol-2-yl]-, hydrochloride (1:1) (CA INDEX NAME)



RN 415684-59-2 CAPLUS
CN Piperazine, 1-[[2-(1,2-dihydro-2-oxo-3-quinolinyl)-1H-indol-5-yl]methyl]-4-(methylsulfonyl)-, 2-hydroxy-1,2,3-propanetricarboxylate (9CI) (CA INDEX NAME)

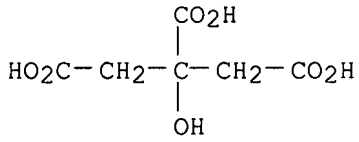
CM 1

CRN 335649-90-6
CMF C23 H24 N4 O3 S



CM 2

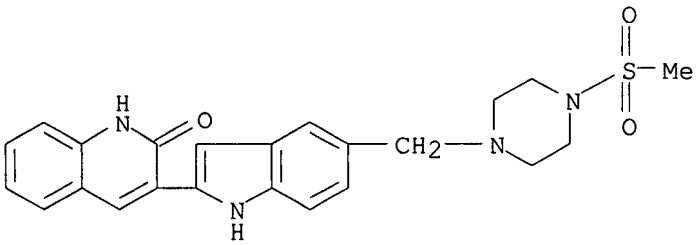
CRN 77-92-9
CMF C6 H8 O7



RN 415684-60-5 CAPLUS
CN Piperazine, 1-[[2-(1,2-dihydro-2-oxo-3-quinolinyl)-1H-indol-5-yl]methyl]-4-(methylsulfonyl)-, monoacetate (9CI) (CA INDEX NAME)

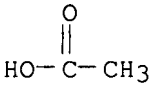
CM 1

CRN 335649-90-6
CMF C23 H24 N4 O3 S

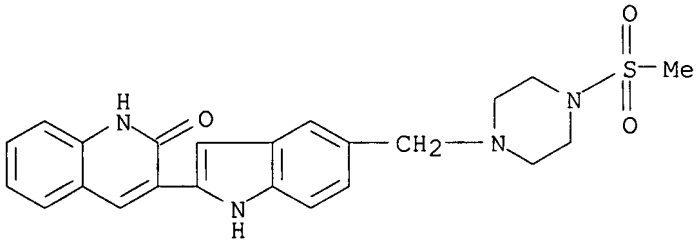


CM 2

CRN 64-19-7
CMF C2 H4 O2



RN 415684-61-6 CAPLUS
CN Piperazine, 1-[[2-(1,2-dihydro-2-oxo-3-quinolinyl)-1H-indol-5-yl]methyl]-4-(methylsulfonyl)-, monohydrobromide (9CI) (CA INDEX NAME)

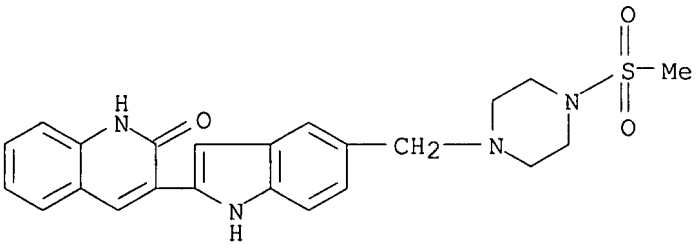


● HBr

RN 415684-62-7 CAPLUS
CN Piperazine, 1-[[2-(1,2-dihydro-2-oxo-3-quinolinyl)-1H-indol-5-yl]methyl]-4-(methylsulfonyl)-, (2Z)-2-butenedioate (9CI) (CA INDEX NAME)

CM 1

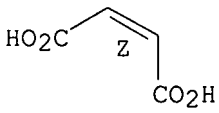
CRN 335649-90-6
CMF C23 H24 N4 O3 S



CM 2

CRN 110-16-7
CMF C4 H4 O4

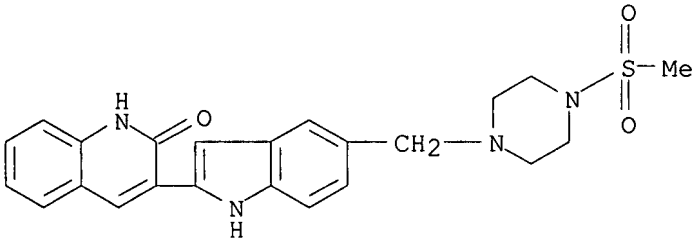
Double bond geometry as shown.



RN 415684-63-8 CAPLUS
CN Piperazine, 1-[[2-(1,2-dihydro-2-oxo-3-quinolinyl)-1H-indol-5-yl]methyl]-4-(methylsulfonyl)-, sulfate (9CI) (CA INDEX NAME)

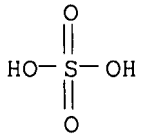
CM 1

CRN 335649-90-6
CMF C23 H24 N4 O3 S



CM 2

CRN 7664-93-9
CMF H2 O4 S

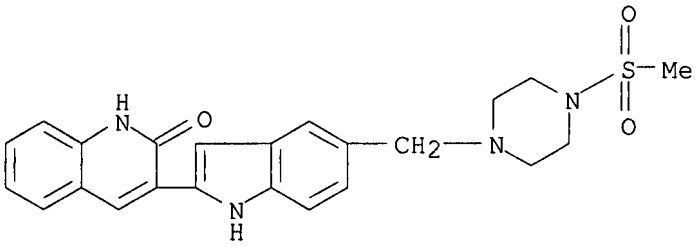


RN 415684-64-9 CAPLUS
CN Piperazine, 1-[[2-(1,2-dihydro-2-oxo-3-quinolinyl)-1H-indol-5-yl]methyl]-4-

(methylsulfonyl)-, monobenzenesulfonate (9CI) (CA INDEX NAME)

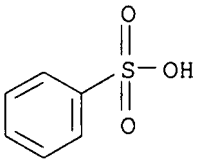
CM 1

CRN 335649-90-6
CMF C23 H24 N4 O3 S



CM 2

CRN 98-11-3
CMF C6 H6 O3 S



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L3              19 S L1 SSS FULL
L4              10 S L3 AND NC>1

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L5               7 S L4

=> s l3 not l4
              15 L3
               7 L4
L6             8 L3 NOT L4

=> d l6 1-8 bib abs hitstr

L6   ANSWER 1 OF 8  CAPLUS  COPYRIGHT 2007 ACS on STN
AN   2006:437069  CAPLUS
DN   144:468020
TI   Process for preparation of 2-substituted indoles from dihalovinylanilines
     and organoboron reagents.
IN   Lautens, Mark; Fang, Yuanqing
PA   Can.
```

10/509078

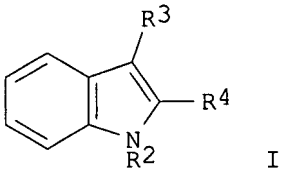
SO PCT Int. Appl., 172 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2006047888	A1	20060511	WO 2005-CA1703	20051104

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRAI US 2004-625102P P 20041105
US 2005-662797P P 20050318
OS MARPAT 144:468020
GI

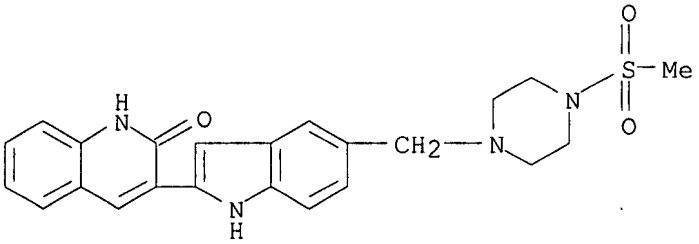


I

AB Title compds. [I; R2 = H, (substituted) alkyl, cycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl; R3 = H, (substituted) alkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, aralkyl, heteroaralkyl; R4 = (substituted) mono- or polycyclic aryl, heteroaryl, alkyl, alkenyl bonded to the 2-position of the indole ring via a C-C bond] were prepared by reaction of ortho-dihalovinylanilines (II; X = Br, Cl, iodo; R2, R3 as above) with boronic esters, boronic acids, boronic acid anhydrides, trialkylboranes, or 9-BBN derivs. of R4 in the presence of base, Pd metal precatalyst, and a ligand. Thus, 2-(2,2-dibromovinyl)phenylamine, PhB(OH)2, K3PO4.H2O, Pd(OAc)2, and s-Phos were heated in PhMe at 90° for 6 h to give 84% 2-phenylindole.

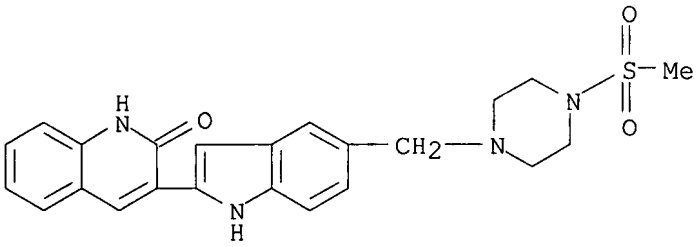
IT 335649-90-6P
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(process for preparation of substituted indoles from dihalovinylanilines and organoboron reagents)

RN 335649-90-6 CAPLUS
CN Piperazine, 1-[[2-(1,2-dihydro-2-oxo-3-quinolinyl)-1H-indol-5-yl]methyl]-4-(methylsulfonyl)- (9CI) (CA INDEX NAME)

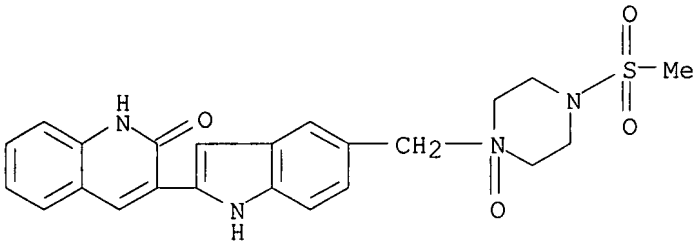


RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

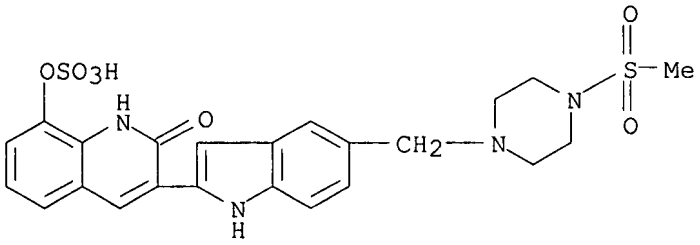
L6 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:571929 CAPLUS
DN 143:298428
TI Induction of CYP1A in the beagle dog by an inhibitor of kinase insert domain-containing receptor: Differential effects in vitro and in vivo on mRNA and functional activity
AU Gibson, Christopher R.; Lin, Charles; Singh, Rominder; Brown, Cheri M.; Richards, Karen; Brunner, Janice; Michel, Kimberly; Adelsberger, Jennifer; Carlini, Edward; Boothe-Genthe, Catherine; Raab, Conrad; Luu, Minh; Michael, Aimee; Parikh, Mona; Ciecko, Patrice; Subramanian, Raju; Krolikowski, Paul; Rodrigues, A. David; Baillie, Thomas A.; Rushmore, Thomas H.
CS Department of Drug Metabolism, Merck Research Laboratories, West Point, PA, USA
SO Drug Metabolism and Disposition (2005), 33(7), 1044-1051
CODEN: DMDSAI; ISSN: 0090-9556
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
AB Compound I [3-[5-(4-methanesulfonyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one] is a potent inhibitor of human kinase insert domain-containing receptor (KDR kinase), which is under investigation for the treatment of cancer. Bile duct-cannulated male beagle dogs were administered 6 mg/kg compound I q.d. for 14 days. There was an approx. 2.5-fold decrease in the mean plasma area under the curve of I on days 7 and 14 (.apprx.11.3 μM · h), relative to day 1 (28.2 μM · h). In the dog, compound I was eliminated by metabolism, with a major pathway being aromatic hydroxylation and subsequent sulfation to form the metabolite M3. Metabolic profiling suggested that the pathway leading to the formation of the sulfated conjugate M3 was induced upon multiple dosing of I. Studies conducted in vitro suggested that CYP1A1/2 was responsible for the formation of the hydroxylated metabolite, which is sulfated to yield M3. Addnl. studies confirmed induction of CYP1A protein and activity in the livers of dogs treated with I. However, studies in a dog hepatocyte model of induction showed a surprising decrease both in CYP1A mRNA and enzymic activity in the presence of I, emphasizing the need to consider the results from a variety of in vitro and in vivo studies in deriving an understanding of the metabolic fate of a drug candidate. It is concluded that the autoinduction observed after multiple treatments with compound I occurs since compound I is both an inducer and a substrate for dog CYP1A.
IT 335649-90-6D, oxygenated 335649-91-7 864852-18-6 864852-20-0 864852-22-2 864852-29-9
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CYP1A activity and mechanism of kinase insert domain-containing receptor inhibitors pharmacokinetics in dog)
RN 335649-90-6 CAPLUS
CN Piperazine, 1-[[2-(1,2-dihydro-2-oxo-3-quinolinyl)-1H-indol-5-yl]methyl]-4-(methylsulfonyl)- (9CI) (CA INDEX NAME)



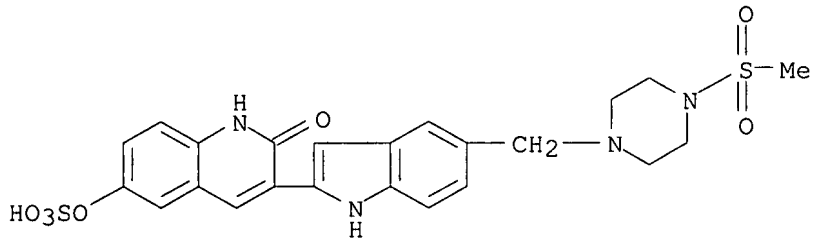
RN 335649-91-7 CAPLUS
CN Piperazine, 1-[[2-(1,2-dihydro-2-oxo-3-quinolinyl)-1H-indol-5-yl]methyl]-4-(methylsulfonyl)-, 1-oxide (9CI) (CA INDEX NAME)



RN 864852-18-6 CAPLUS
CN Piperazine, 1-[[2-[1,2-dihydro-2-oxo-8-(sulfooxy)-3-quinolinyl]-1H-indol-5-yl]methyl]-4-(methylsulfonyl)- (9CI) (CA INDEX NAME)

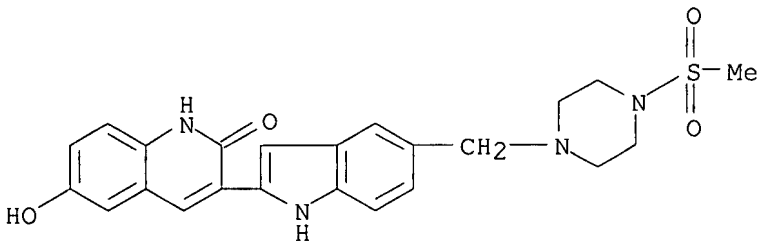


RN 864852-20-0 CAPLUS
CN Piperazine, 1-[[2-[1,2-dihydro-2-oxo-6-(sulfooxy)-3-quinolinyl]-1H-indol-5-yl]methyl]-4-(methylsulfonyl)- (9CI) (CA INDEX NAME)

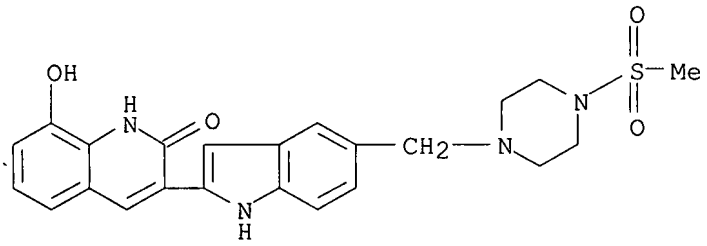


RN 864852-22-2 CAPLUS
CN 2(1H)-Quinolinone, 6-hydroxy-3-[5-[[4-(methylsulfonyl)-1-

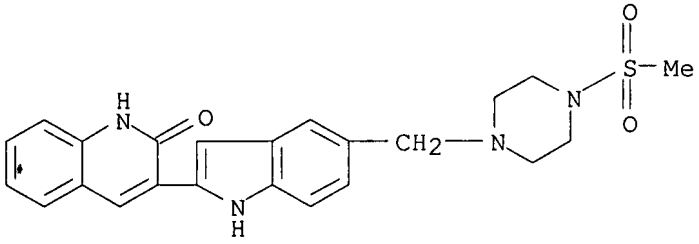
piperazinyl]methyl]-1H-indol-2-yl]- (9CI) (CA INDEX NAME)



RN 864852-29-9 CAPLUS
CN 2(1H)-Quinolinone, 8-hydroxy-3-[5-[[4-(methylsulfonyl)-1-piperazinyl]methyl]-1H-indol-2-yl]- (9CI) (CA INDEX NAME)



IT 335649-90-6, [3-[5-(4-Methanesulfonyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one]
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CYP1A activity and mechanism of kinase insert domain-containing receptor inhibitors pharmacokinetics in dog)
RN 335649-90-6 CAPLUS
CN Piperazine, 1-[[2-(1,2-dihydro-2-oxo-3-quinolinyl)-1H-indol-5-yl]methyl]-4-(methylsulfonyl)- (9CI) (CA INDEX NAME)



RE.CNT 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:174313 CAPLUS
DN 142:309130
TI Concerns in the development of an assay for determination of a highly conjugated adsorption-prone compound in human urine
AU Xu, Yang; Du, Lihong; Rose, Mark J.; Fu, Irong; Woolf, Eric J.; Musson, Donald G.
CS Merck Research Laboratories, West Point, PA, 19486, USA

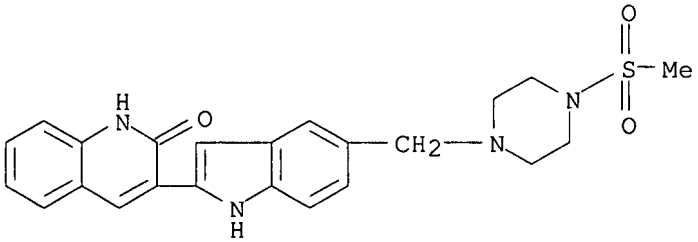
SO Journal of Chromatography, B: Analytical Technologies in the Biomedical and Life Sciences (2005), 818(2), 241-248
CODEN: JCBAAI; ISSN: 1570-0232
PB Elsevier B.V.
DT Journal
LA English

AB Concerns in pre-anal. handling of urine samples are discussed using a new KDR kinase inhibitor, 3-[5-(4-methanesulfonyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one (compound A), as an example of a case where high light sensitivity and low analyte recovery (high affinity for container surface) were found. The absence of these problems in plasma samples may be a result of the plasma protein content. Low recovery of the analyte from urine can be remedied by either changing the container or by using additives, such as bovine serum albumin (BSA) or non-ionic surfactant Tween-20. In the case of compound A, changing containers (polypropylene vs. glass vial) or addition of BSA did bring analyte recovery up to 80%. However, the addition of 0.2% Tween-20 into urine quality controls (QCs) gave more than 95% analyte recovery, indicating effective reduction of analyte loss to the surface of containers. The urine assay using mixed-mode SPE and LC-MS/MS was not affected significantly by introducing Tween-20 into the samples. The mean SPE extraction recovery was 68.4% and matrix suppression of ionization on MS was less than 8% at all analyte concns. The linear range of the calibration curve was 0.5-400 ng/mL on PE Sciex API 3000 LC-MS/MS system. The assay intraday accuracy and precision were 92.1-104.8% and <4.2% (%CV), resp. Urine QC samples, containing 0.2% Tween-20, gave excellent recovery after three cycles of freeze and thaw. Since analyte loss to its urine container surface is not unique to compound A (M. Schwartz, W. Kline, B. Matuszewski, Anal. Chim. Acta 352 (1997) 299-307; A. L. Fisher, E. DePuy, T. Shih, R. Stearns, Y. Lee, K. Gottesdiener, S. Flattery, M. De Smet, B. Keymeulen, D. G. Musson, J. Pharm. Biomed. Anal. 26 (2001) 739-752), we suggest an evaluation of the potential problem in the early stages of urine assay development to ensure reliable quantitation of analytes. The addition of Tween-20 can serve as a useful anal. tool to other analytes with similar situations.

IT 335649-90-6, 3-[5-(4-Methanesulfonyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one
RL: ANT (Analyte); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study)
(concerns in development of an assay for determination of highly conjugated adsorption-prone compound in human urine)

RN 335649-90-6 CAPLUS

CN Piperazine, 1-[[2-(1,2-dihydro-2-oxo-3-quinolinyl)-1H-indol-5-yl]methyl]-4-(methylsulfonyl)- (9CI) (CA INDEX NAME)



RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:85916 CAPLUS
DN 142:328833
TI Simultaneous determination of a novel KDR kinase inhibitor and its N-oxide

metabolite in human plasma using 96-well solid-phase extraction and liquid chromatography/tandem mass spectrometry

AU Xu, Yang; Du, Lihong; Soli, Eric D.; Braun, Matthew P.; Dean, Dennis C.; Musson, Donald G.

CS Merck Research Laboratories, Department of Drug Metabolism, West Point, PA, 19486, USA

SO Journal of Chromatography, B: Analytical Technologies in the Biomedical and Life Sciences (2005), 817(2), 287-296
CODEN: JCBAAI; ISSN: 1570-0232

PB Elsevier B.V.

DT Journal

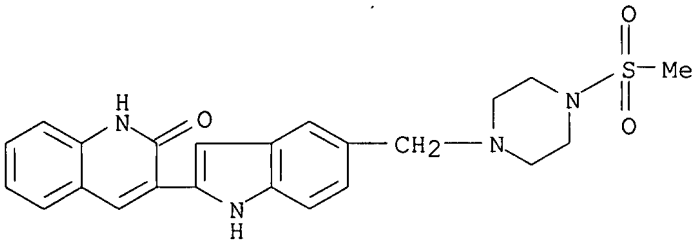
LA English

AB To support pharmacokinetic studies, a selective and sensitive liquid chromatog./tandem mass spectrometry (LC-MS/MS) method was developed and validated for the simultaneous determination of a novel KDR kinase inhibitor (1) and its active metabolite (2) in human plasma. The method is fully automated using a Packard MultiPROBE II system and a TomTec Quadra 96 liquid handling workstation to perform sample preparation and solid-phase extraction (SPE). Following the extraction on a mixed-mode SPE using Oasis MCX 96-well plate, the analytes were separated on a Aquasil C18 column (50 mm × 2.1 mm, i.d., 3 μm) with a mobile phase consisting of acetonitrile/ammonium acetate buffer (5 mM, pH 5.0) (60/40, volume/volume). The run time for each injection was 4.5 min with the retention times of approx. 2.0 and 2.7 min for 1 and 2 resp., at a flow rate of 0.25 mL/min. A tandem mass spectrometric detection was conducted using multiple reaction monitoring (MRM) under the pos. ion mode with a turbo ion-spray interface. The linear ranges of the calibration curves were 0.05-400 ng/mL for 1 and 0.1-400 ng/mL for 2 on a PE Sciex API 4000 LC-MS/MS system. The lower limits of quantitation (LLOQ) of the assay were 0.05 and 0.1 ng/mL for 1 and 2 resp., when 0.4 mL of plasma was processed. Intra-day assay precision (using 5 standard curves prepared by spiking compds. to 5 lots of plasma) was < 4.9% for 1 and < 9.6% for 2 on each concentration Assay accuracy was found to be 95.1-104.6% of nominal for 1 stds. and 93.5-105.6% for 2 stds. QC samples were stable when kept at room temperature for 4 h, at -70 °C for 10 days, and after 3 freeze-thaw cycles. The extraction recoveries were 80, 83, and 84% for 1 and 2 and I.S. resp., and no significant matrix effects were observed The method was successfully applied to plasma samples from clin. studies after oral administration of compound 1.

IT 335649-90-6 335649-91-7
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(simultaneous determination of novel KDR kinase inhibitor and its N-oxide metabolite in human plasma by LC-MS/MS)

RN 335649-90-6 CAPLUS

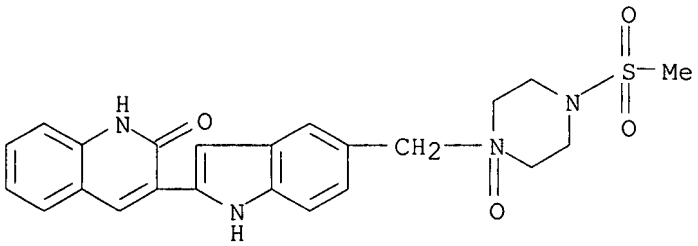
CN Piperazine, 1-[[2-(1,2-dihydro-2-oxo-3-quinolinyl)-1H-indol-5-yl]methyl]-4-(methylsulfonyl)- (9CI) (CA INDEX NAME)



RN 335649-91-7 CAPLUS

CN Piperazine, 1-[[2-(1,2-dihydro-2-oxo-3-quinolinyl)-1H-indol-5-yl]methyl]-4-

(methylsulfonyl)-, 1-oxide (9CI) (CA INDEX NAME)



RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:14366 CAPLUS
DN 142:113888
TI Substituted indoles and a process for their preparation via Pd/diamine-catalyzed reductive cyclization of ortho-nitrostyrenes under CO pressure
IN Davies, Ian W.; Smitrovich, Jacqueline H.; Qu, Chuanxing
PA Merck & Co., Inc., USA
SO PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005000804	A2	20050106	WO 2004-US17357	20040601
	WO 2005000804	A3	20050804		
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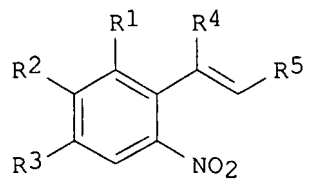
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2004251175	A1	20050106	AU 2004-251175	20040601
	CA 2526988	A1	20050106	CA 2004-2526988	20040601
	EP 1633694	A2	20060315	EP 2004-776226	20040601
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
	CN 1798726	A	20060705	CN 2004-80015534	20040601
	JP 2006526654	T	20061124	JP 2006-515094	20040601
	US 2007054921	A1	20070308	US 2005-557537	20051121
PRAI	US 2003-476089P	P	20030605		
	WO 2004-US17357	W	20040601		

OS CASREACT 142:113888; MARPAT 142:113888
GI



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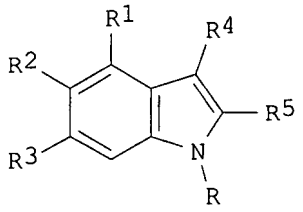

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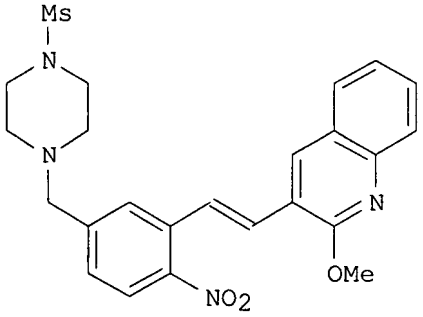

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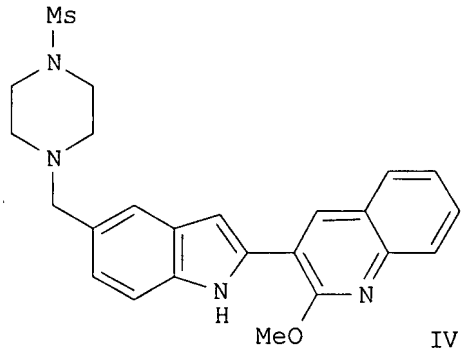


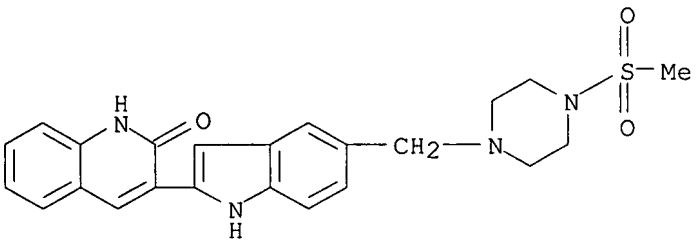
IV

AB The invention is directed to novel compds. I and II as well as a process for the preparation of II from I, via palladium-catalyzed reductive cyclization of I under CO pressure with aromatic diamines as ligands, wherein R1 = H, (un)substituted alkyl or alkoxy; R2 = H, (un)substituted alkyl, alkoxy or halo; R3 = H, (un)substituted alkyl or alkoxy; R2 and R3 can link together; R4 = H, (un)substituted alkyl, alkoxy or ester; R5 = (un)substituted alk(en/yn)yl, (hetero)aryl, amide or ketone; R = H or OH; or salts thereof. For example, An autoclave was charged with III (15 g, preparation given), Pd(OTf)2 (0.020 g), 3,4,7,8-tetramethyl-1,10-phenathroline (0.102 g) and DMF (100 mL). After the vessel was purged three times successively with N2 and CO, the reactor was pressurized to 15 psig with CO and aged at 70 °C for 14 h. IV was isolated in 83 % yield after work-up. The new process can be conducted under milder conditions, such as lower temperature and CO pressure, as well as lower catalyst and ligand loading, which simplify purification II are useful intermediates of pharmaceutical compds., such as KDR inhibitors and GNRH inhibitors (no data).

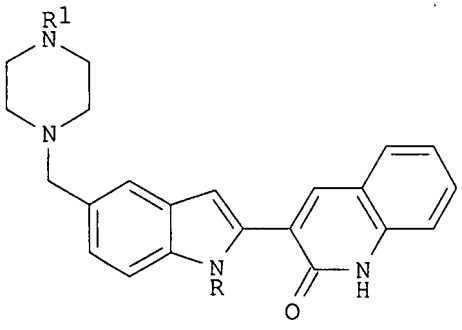
IT 335649-90-6P
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(target; preparation of indoles via Pd/diamine-catalyzed reductive cyclization of ortho-nitrostyrenes under CO pressure)

RN 335649-90-6 CAPLUS

CN Piperazine, 1-[[2-(1,2-dihydro-2-oxo-3-quinolinyl)-1H-indol-5-yl]methyl]-4-(methylsulfonyl)- (9CI) (CA INDEX NAME)



L6 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:1005650 CAPLUS
DN 142:134559
TI A Concise Synthesis of a Novel Antiangiogenic Tyrosine Kinase Inhibitor
AU Payack, Joseph F.; Vazquez, Enrique; Matty, Louis; Kress, Michael H.; McNamara, James
CS Department of Process Research, Merck & Co. Inc., Rahway, NJ, 07065-0900, USA
SO Journal of Organic Chemistry (2005), 70(1), 175-178
CODEN: JOCEAH; ISSN: 0022-3263
PB American Chemical Society
DT Journal
LA English
OS CASREACT 142:134559
GI



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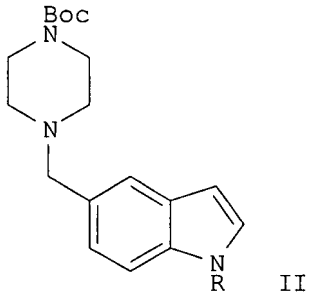
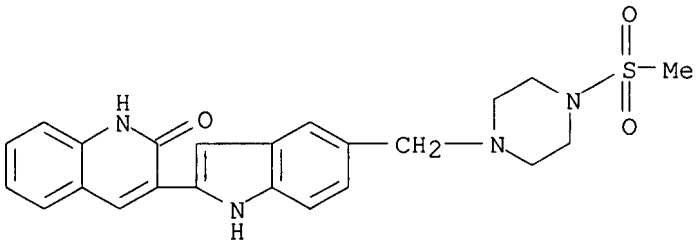


II

AB Antiangiogenic compound I (R = H; R1 = MeSO2) (an inhibitor of the endothelial VEGF receptor KDR) is prepared concisely and efficiently on kilogram scale using the Suzuki-Miyaura coupling of a boronic acid generated in situ from Boc-protected indolemethylpiperazine II (Boc = Me3COCO) with 3-bromoquinolin-2-one as the key step. 5-Cyanoindole is Boc protected at the indole nitrogen, reduced to the aldehyde with DIBAL, and reductively aminated with Boc-piperazine using sodium triacetoxyborohydride to yield II. Methyltrioxorhenium-mediated oxidation of 3-bromoquinoline followed by rearrangement of the N-oxide with p-toluenesulfonyl chloride yields 3-bromoquinolin-2-one. Lithiation of II with LDA at <5° followed by addition of triisopropyl borate and quenching with hydrochloric acid yields a 2-indoleboronic acid which is coupled with 3-bromoquinolin-2-one in the presence of palladium acetate, triphenylphosphine, and dicyclohexylamine to yield I (R = R1 = Boc) in 88% yield. Cleavage of the Boc groups with hydrochloric acid followed by mesylation of the piperazine yields I (R = H; R1 = MeSO2).

IT 335649-90-6P
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(concise preparation of an antiangiogenic compound on kilogram scale using a Suzuki-Miyaura coupling of an indoleboronic acid (generated in situ) and a bromoquinolinone as the key step)
RN 335649-90-6 CAPLUS
CN Piperazine, 1-[[2-(1,2-dihydro-2-oxo-3-quinolinyl)-1H-indol-5-yl]methyl]-4-(methylsulfonyl)- (9CI) (CA INDEX NAME)

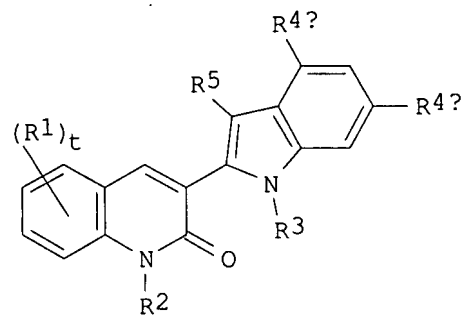


RE.CNT 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2003:202476 CAPLUS
DN 138:238026
TI Preparation of indolinylquinolinones as tyrosine kinase inhibitors with therapeutic uses
IN Kim, Yuntae; Hanney, Barbara; Spencer, Keith L.; Hartman, George D.; Arrington, Kenneth L.
PA Merck & Co., Inc., USA
SO PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003020276	A1	20030313	WO 2002-US27161	20020826
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2002326760	A1	20030318	AU 2002-326760	20020826
	US 2004192725	A1	20040930	US 2004-487588	20040224
	US 6927293	B2	20050809		
PRAI	US 2001-315897P	P	20010830		
	WO 2002-US27161	W	20020826		

OS MARPAT 138:238026
GI



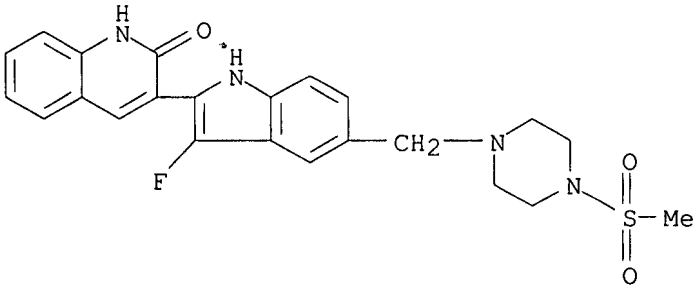
I

AB The present invention relates to indolinylquinolinones (shown as I; variables defined below; e.g. 3-[6-[(4-methylpiperazin-1-yl)carbonyl]-1H-indol-2-yl]quinolin-2(1H)-one) which inhibit, regulate and/or modulate tyrosine kinase signal transduction, compns. which contain these compds., and methods of using them to treat tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals. For I: a = 0 or 1; b = 0 or 1; n = 0, 1, or 2; t = 1 or 2; R1 and R5 = H, (C:O)aObC1-C10 alkyl, (C:O)aObaryl, (C:O)aObC2-C10 alkenyl, (C:O)aObC2-C10 alkynyl, CO2H, halo, OH, ObC1-C6 perfluoroalkyl, (C:O)aNR7R8, CN, (C:O)aObC3-C8 cycloalkyl, and (C:O)aObheterocyclyl. R2 and R3 = H, (C:O)OaC1-C6 alkyl, (C:O)Oaaryl, C1-C6 alkyl, SO2Ra, and aryl; R4a or R4b = H and the other = (C:O)aObC1-C10 alkyl, (C:O)aObaryl, (C:O)aObC2-C10 alkenyl, (C:O)aObC2-C10 alkynyl, CO2H, halo, OH, ObC1-C6 perfluoroalkyl, (C:O)aNR7R8, CN, (C:O)aObC3-C8 cycloalkyl, and (C:O)aObheterocyclyl. R7 and R8 = H, (C:O)ObC1-C10 alkyl, (C:O)ObC3-C8 cycloalkyl, (C:O)Obaryl, (C:O)Obheterocyclyl, C1-C10 alkyl, aryl, C2-C10 alkenyl, C2-C10 alkynyl, heterocyclyl, C3-C8 cycloalkyl, SO2Ra, (C:O)N(Rb)2, or R7 and R8 can be taken together with the N to which they are attached to form a monocyclic or bicyclic heterocycle with 5-7 members in each ring and optionally containing, in addition to the N, one or two addnl. heteroatoms = N, O and S; Ra = (C1-C6)alkyl, (C3-C6)cycloalkyl, aryl, or heterocyclyl; and Rb is H, (C1-C6)alkyl, aryl, heterocyclyl, (C3-C6)cycloalkyl, (C:O)OC1-C6 alkyl, (C:O)C1-C6 alkyl or S(O)2Ra. Compds. I inhibit VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 values = 0.01-5.0 μM. Although the methods of preparation are not claimed, 3 example prepns. are included.

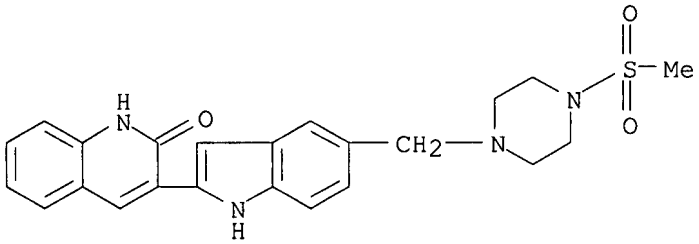
IT 501364-54-1P, 3-[3-Fluoro-5-(4-methanesulfonylpiperazin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of indolinylquinolinones as tyrosine kinase inhibitors with therapeutic uses)

RN 501364-54-1 CAPLUS

CN Piperazine, 1-[[2-(1,2-dihydro-2-oxo-3-quinolinyl)-3-fluoro-1H-indol-5-yl]methyl]-4-(methylsulfonyl)- (9CI) (CA INDEX NAME)



IT 335649-90-6, 3-[5-[[4-(Methylsulfonyl)piperazin-1-yl]methyl]-1H-indol-2-yl]quinolin-2(1H)-one
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of indolinylquinolinones as tyrosine kinase inhibitors with therapeutic uses)
RN 335649-90-6 CAPLUS
CN Piperazine, 1-[[2-(1,2-dihydro-2-oxo-3-quinolinyl)-1H-indol-5-yl]methyl]-4-(methylsulfonyl)- (9CI) (CA INDEX NAME)



RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2001:300706 CAPLUS
DN 134:326411
TI Preparation of 3-(2-indolyl)quinoline-2-one derivatives as tyrosine kinase inhibitors
IN Arrington, Kenneth L.; Bilodeau, Mark T.; Fraley, Mark E.; Hartman, George D.; Hoffman, William F.; Hungate, Randall W.; Kim, Yuntae
PA Merck & Co., Inc., USA
SO PCT Int. Appl., 130 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001029025	A2	20010426	WO 2000-US28625	20001016
	WO 2001029025	A3	20011101		

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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

	CA 2387351	A1	20010426	CA 2000-2387351	20001016
	BR 2000014843	A	20020611	BR 2000-14843	20001016
	EP 1226136	A2	20020731	EP 2000-978230	20001016
	EP 1226136	B1	20041229		
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	HU 200203323	A2	20030228	HU 2002-3323	20001016
	JP 2003512369	T	20030402	JP 2001-531825	20001016
	JP 3822494	B2	20060920		
	EE 200200201	A	20030616	EE 2002-201	20001016
	NZ 518001	A	20040528	NZ 2000-518001	20001016
	AU 778588	B2	20041209	AU 2001-15710	20001016
	AT 286045	T	20050115	AT 2000-978230	20001016
	PT 1226136	T	20050429	PT 2000-978230	20001016
	ES 2234698	T3	20050701	ES 2000-978230	20001016
	US 6306874	B1	20011023	US 2000-690598	20001017
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	ZA 2002002985	A	20030416	ZA 2002-2985	20020416
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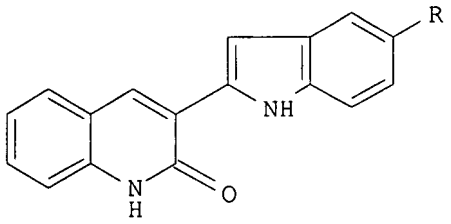
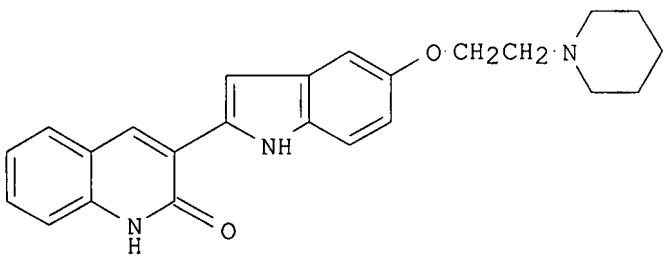
	US 6794393	B1	20040921	US 2002-110872	20020418
	BG 106710	A	20030331	BG 2002-106710	20020516
	HK 1054931	A1	20060317	HK 2003-107148	20031003
	US 2005096344	A1	20050505	US 2004-900662	20040728
	JP 2006206609	A	20060810	JP 2006-127244	20060501
PRAI	US 1999-160356P	P	19991019		
	JP 2001-531825	A3	20001016		
	WO 2000-US28625	W	20001016		
	US 2000-690598	A	20001017		
	US 2002-110872	A1	20020418		

OS MARPAT 134:326411

GI



I



II

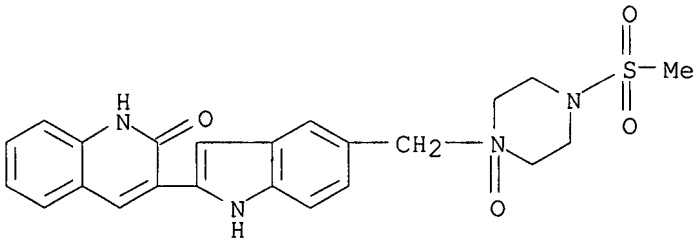
AB Title compds. [I; R = (CH3)2NCH2CH(CH3)CH2O, (CH3OCH2CH2)(C6H5CH2)NCH2CH2O, (CH3CH2)2NCH2CH2O, (CH3)(C6H5CH2)NCH2CH2CH2O, (CH3OCH2CH2)(HOOCCH2CH2)NCH2CH2O, (CH3OCH2CH2)(CH3SO2)NCH2, cycloalkylaminoalkyl, heterocyclylalkyl, etc.], stereoisomer, and pharmaceutically acceptable salts are prepared and inhibit, regulate and/or modulate tyrosine kinase signal transduction. Title compds. are tested on

VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 values between 0.001-5.0 μM. Pharmaceutical compns. and methods of using them to treat tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, etc. are discussed. Thus, the title compound II was prepared

IT 335649-91-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 3-(2-indolyl)quinoline-2-one derivs. as tyrosine kinase inhibitors)

RN 335649-91-7 CAPLUS

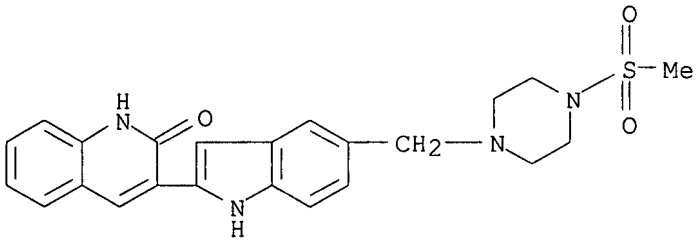
CN Piperazine, 1-[[2-(1,2-dihydro-2-oxo-3-quinolinyl)-1H-indol-5-yl]methyl]-4-(methylsulfonyl)-, 1-oxide (9CI) (CA INDEX NAME)



IT 335649-90-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of 3-(2-indolyl)quinoline-2-one derivs. as tyrosine kinase inhibitors)

RN 335649-90-6 CAPLUS

CN Piperazine, 1-[[2-(1,2-dihydro-2-oxo-3-quinolinyl)-1H-indol-5-yl]methyl]-4-(methylsulfonyl)- (9CI) (CA INDEX NAME)



=> log h

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	81.87	262.28

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-11.70	-11.70

SESSION WILL BE HELD FOR 120 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 19:57:59 ON 20 MAY 2007